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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper number 071604

Application Number: 09/833,782
Filing Date: 4/12/2001
Appellant(s): D. Wade Walke, *et al.*

Lance K. Ishimoto
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed originally Sept. 29, 2003, a copy filed March 17, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

Appellant's brief includes a statement that there are no related appeals or interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is not exact for the following reasons.

In the First Office Action issued on January 18, 2002, claims 1-3 were rejected under 35 USC § 101 as lacking patentable utility, and under 35 USC § 112, first

paragraph as unusable due to lack of patentable utility. Claim 2 was also rejected under 35 USC § 112, second paragraph as indefinite and **claim 1** (in the First Action inadvertently mentioned as claim 3) was rejected under 35 USC §102 (b).

It is not mentioned that in the First Action claim 1 was also rejected under 35 USC § 112, first paragraph, for lack of written description and enablement.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is confusing for the following reasons.

1. **Appellants state they disclose novel human sequences that encode a human metalloprotease, neurolysin.**

Although the function of the disclosed protein (SEQ ID NO: 2) is asserted to be a metalloprotease (see the title), nowhere in the specification do Appellants assert the protein is neurolysin. Appellants indicate "a protein sharing sequence similarity with mammalian neurolysin proteins", page 1, line 10, which is a statement related to the structure of the novel polypeptide and not to its function.

2. **Appellants state they disclose, "naturally occurring polymorphisms that exist within these molecules (page 16, lines 21-28)", Appeal Brief page 3, line 6.**

The fragment on page 16, lines 21-28 of the specification reads as follows:

> "will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.
>
> When it is desired that a NHP [novel human protein] transgene be integrated into the chromosomal site of the endogenous NHP gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous NHP gene are designed for the purpose of integrating, via homologous recombination with"

and is not related to a polymorphism.

3. **Appellants also inform "Appellants have used the methods described in the specification as filed (page 2, lines 11-32 and page 17, lines 17-23) to construct knockout mice", page 3, line 11 of the Appeal Brief.**

The fragment on page 17, lines 17-23 reads as follows:

> "The described NHP, NHP polypeptides, NHP peptide fragments, mutated, truncated, or deleted forms of the NHP and/or NHP fusion proteins can be prepared for a variety of uses. These uses include, but are not limited to, the generation of antibodies, as reagents in diagnostic assays, the identification of other cellular gene products related to",

and is not related to constructing a knockout mice.

4. Appellants refer to assessing temporal and tissue specific gene expression, "Additional uses for the sequences of the present invention include assessing temporal and tissue specific gene expression patterns (specification at page 6, line 24)", page 3, line 16 of the Appeal Brief.

The fragment on page 6, line 24 of the specification reads as follows:

> "not overlap. Accordingly, the described polynucleotide sequences shall typically comprise at least about two or three distant oligonucleotide sequences"

and is not related to assessing temporal and tissue specific gene expression patterns. Nowhere in the specification do Appellants disclose temporal expression pattern [i.e. expression of SEQ ID NO: 1 or 3 depending on the age of tissue or time of cultivation of cells in culture or time after any specific treatment of the culture]. As to the tissue expression pattern, Appellants only teach on page 3, line 12 that NHP is expressed in many human tissues. However, the specification does not teach the absolute values of the expression levels in these tissues nor relative values of expression in different tissues, which is called in the art tissue expression pattern.

5. Appellants refer to the use of novel genes in "mapping the sequences to a specific region of human chromosome and identifying protein encoding regions (specification at page 11, line 11-17)", page 3, line 19 of the Appeal Brief.

The fragment on page 11, line 11-17 reads as follows:

"amplified fragment for the priming of the first strand synthesis. The resulting RNA/DNA hybrid may then be 'tailed' using a standard terminal transferase reaction, the hybrid may be digested with RNAse H, and second strand synthesis may then be primed with a complementary primer. Thus, cDNA sequences upstream amplified fragment can be isolated",

and is not related to mapping claimed DNA sequences on a human chromosome but to isolation of a full length cDNA sequence by translating the cellular RNA to cDNA and its subsequent multiplication.

6. Appellants emphasize the use of the claimed DNA sequences in "determining genomic structure, (specification page 11, line 5-11)", page 3, line 21 of the Appeal Brief.

The fragment on page 11, line 5-11 of the specification reads as follows:

"PCR technology can be used to isolate full length cDNA sequences. For example, RNA can be isolated, following standard procedures, from an appropriate cellular or tissue source (i.e., one known, or suspected, to express a NHP gene, such as, for example, testis tissue). A reverse transcription (RT) reaction can be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis",

and does not enable one skilled in the art to determine the genomic structure of gene encoding NHP but isolation of a cDNA sequence.

7. Appellants stress the use of the claimed DNA sequences in "forensic analysis, human population biology and paternity determinations (see, for example, the specification from page 11, line

5-17) wherein the sequences of the present invention are particularly useful as the specification identified polymorphisms (page 16, line 21-28) that can be used in these assays", page 3, line 22 of the Appeal Brief.

The fragment on page 11, line 5-17 reads as follows:

> "PCR technology can be used to isolate full length cDNA sequences. For example, RNA can be isolated, following standard procedures, from an appropriate cellular or tissue source (i.e., one known, or suspected, to express a NHP gene, such as, for example, testis tissue). A reverse transcription (RT) reaction can be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis. The resulting RNA/DNA hybrid may then be 'tailed' using a standard terminal transferase reaction, the hybrid may be digested with RNAse H, and second strand synthesis may then be primed with a complementary primer. Thus, cDNA sequences upstream amplified fragment can be isolated",

and is not related to the use of claimed polynucleotide sequences in forensic analysis, human population biology and paternity determination. Regarding he identification of polymorphism, as indicated above, the specification does not identify the polymorphisms on page 16, line 21-28, because said fragment of the specification is not related to any polymorphism.

8. Closing the paragraph V. Summary of the Invention, Appellants conclude: "The sequences of the present invention encode neurolysin, a protein of known function and Appellants have used methods described in the specification (page 2 lines 11-32 and

page 17, lines 17-23) as filed to biologically validate their assertions that the sequence of the present invention have utility as drug targets for human diseases (specification page 1, lines 27-31) among other utilities", Appeal Brief, page 3 line 25 and further.

As indicated above, nowhere in the specification can the reader find the assertion that the new sequences encode a neurolysin. As to the methods Appellants are referring to, it seems Appellants mean enhancing the expression of the described polynucleotides by placing them under the control of a strong promoter, and obtaining transgenic animals that express a NHP transgene. However, the specification does not disclose any results corroborating utility of present sequences as drug targets in any transgenic model of human diseases enumerated on page 1 of the specification.

(6) Issues

The Appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Kato et al., Biol. Chem. 1997, vol. 272, pp. 15313-15322.

Chen et al., GenBank accession number AJ300837 (polynucleotide sequence), January 2001.

Chen et al., GenBank accession number CAC27329 (amino acid sequence), January 2001.

Venter et al., Science 2001, vol. 291, pp. 1304-1351.

Jasny and Kennedy, Science 2001, vol. 291, p. 1153.

Schrimpton et al., Endocr. Rev. 2002, vol. 23/5, pp. 647-664 (abstract).

Norman et al., Am. J. Physiol. Heart Circ. Physiol. 2003, vol. 284/6, pp. 1978-1984 (abstract).

Bork et al., Genome Research, 2000, vol. 10, pp. 398-400.

Smith et al., Nature Biotechnology, 1997,vol. 15, pp. 1222-1223.

Brenner, TIG, 1999 vol. 15, pp.1332-1333.

Broun et al. Science 1998, vol. 282, pp. 1315-1317.

Seffernick J. et al., J. Bact. 2001, vol. 183, pp. 2405-2410.

Whiststock et al. Quart. Rev. Biophys. 2003, vol. 36/3, pp. 307-340.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 1-5 are directed to isolated polynucleotide of SEQ ID NO: 1 encoding protein of SEQ ID NO: 2. The specification discloses that the claimed polynucleotide encodes a protein, which shares structural similarities with mammalian neurolysin and angiotensin binding proteins; see page 1, line 10 and page 2, line 7. The exact language used on page 1of the specification is:

> "The present invention relates to the discovery, identification, and characterization of novel human polynucleotides [open reading frame of SEQ ID NO: 1, end open reading frame with flanking sequences set forth by SEQ ID NO: 3] encoding a protein sharing sequence similarity with mammalian neurolysin proteins [the percentage of similarity to any neurolysin is not stated in the specification]"

The exact language used on page 2 of the specification is:

> "The present invention relates to the discovery, identification, and characterization of nucleotides [sic!] that encode a novel human protein, and the corresponding amino acid sequence of this protein. The novel human protein (NHP) described for the first time herein shares structural similarity with animal neurolysins and angiotensin-binding proteins [the percentage of similarity to any angiotensin-binding protein is not quoted in the specification]."

Appellants, however, do not assert the function of the encoded protein as being that of neurolysin. Nowhere in the specification is there any statement that suggests that the disclosed protein shares functional similarity to mammalian neurolysins. An assertion of structural similarity is not an assertion of functional similarity, as it is well

known in the art that very similar structures may have distinct functions (for example many single amino acid changes in proteins completely abolish the function of the protein). While it is also true that completely unrelated structures may have similar function.

There is no experimental evidence in the specification to support the notion the claimed polynucleotides encode a polypeptide having neurolysin function, and the only assertion of function in the specification merely asserts that the disclosed protein is a metalloprotease. The alleged function for the claimed polynucleotides has been determined solely on the basis of structural similarity (i.e. sequence homology) with mammalian neurolysins known in the art, however, no quotation is provided of the percentage of homology to any mammalian neurolysin known at the time the application was filed. The phrase "sharing sequence similarity with mammalian neurolysin proteins" is not the statement of function, but it refers to the structure of the claimed chemical compound. At the time application was filed the function of neurolysin was well established for mammals, as Applicants proved by the content of the IDS. The characteristic features of neurolysin is that it cleaves neurotensin between residues Pro10 and Tyr11, and that it binds angiotensin. Appellants themselves did not present any evidence that protein of SEQ ID NO: 2 is able to cleavage neurotensin between residues Pro10 and Tyr11, and to bind angiotensin. Furthermore, the state of the art clearly teaches the unpredictability of assigning function based on sequence homology and acknowledges that small changes in amino acid sequence can drastically change function. Bork (Genome Research, 10:398-400, 2000), Smith et al. (Nature

Biotechnology 15:1222-1223, 1997) and Brenner (TIG 15:132-1333, 1999) are some of the references which describe the overall state of the art in regard to the unpredictability of annotating function.

There are numerous cases in which proteins of very different functions are homologous. Examples of pitfalls associated with comparative sequence analysis for predicting function are shown by Broun et al. (Science 282:1315-1317, 1998). Broun et al. teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Other example that **two proteins with homology as high as 98% may have different functions is reported** by Seffernick J. et al, J. Bact. 2001, Vol. 183, pp. 2405-2410. In the recent review Whiststock et al. summarize, "prediction of protein function from sequence and structure is a difficult problem, because homologous proteins often have different functions"; see the abstract.

The specification also asserts that the claimed polynucleotides can be used as 1) hybridization probes for screening libraries and assessing gene expression patterns in microarrays or high-throughput chip format (page 5 line 18), 2) for localizing their position on human chromosome (page 2, line 33), or 3) for treatment or diagnosis of physiological disorders or diseases (page 1, line 19). These utilities, however, are not considered substantial and specific, because the specification fails to disclose sufficient information regarding biological function and significance of the claimed polynucleotides and the protein encoded thereby.

The use as hybridization probes for screening libraries and assessing gene expression patterns in microarrays or high-throughput chip format is not considered substantial and specific because it is proper for any polynucleotide or any expressed polynucleotide and this use does not involve the specific biological role of the claimed polynucleotide. Similarly, mapping a polynucleotide obtained from any eukaryotic cell to its chromosome is not specific and substantial utility because it is proper for any polynucleotide even that which encodes a nonsense genetic information.

The invention cannot be used for treatment and diagnosing abnormalities related to human diseases because lack of disclosure of its biological role does not allow identifying in which human physiological abnormalities the claimed polynucleotides are involved. For that reason the art knowledge about other mammalian neurolysins does not establish utility for the disclosed human gene.

Claim Rejections - 35 USC §112, first paragraph

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(11) Response to Argument

A. Do Claims 1 -5 lack a patentable utility?

I. Beginning at the 19th line of page 3 of the Brief, Appellants direct the reader's attention to "novel nucleic acid and amino acid sequences, their tissue expression pattern and naturally occurring polymorphism (page 16, lines 21-28)". Continuing Appellant state, "the sequences of the present invention encode neurolysin, a protein of known function and Appellants have used methods described in the specification (page 2, lines 11-32 and page 17, lines 17-23 as filled to biologically validate their assertions that the sequence of the present invention have [!] utility as drug targets for human disease (specification at page 1, lines 27-31)."

Reply The sequences are novel, however, Appellants do not provide their tissue expression pattern because enumerating the tissues in which the expression was observed is not what one skilled in the art calls an expression pattern; see above in the paragraph ***(6) Summary of Invention***, point 4. As to the polymorphism of SEQ ID NO: 1, Appellants indicate its polymorphism on page 15, line 14 and not on page 16.

Nowhere in the application one can find the quoted above assertion "the sequences of the present invention encode neurolysin". Appellants refer to "a protein sharing sequence similarity [emphasis added] with mammalian neurolysin proteins", page 1, line 10, and on page 2 line 5 of the specification they indicate "the novel human protein (NHP) described for the first time herein shares structural similarity [emphasis added] with animal neurolysins and angiotensin-binding proteins." Both statements are related to the structure of the novel polypeptide and not to its function.

II. Appellants assure they used methods described in the specification as filed (page 2, lines 11-32, describes in general terms construction of a knock-out mice, and page 17, lines 17-23 refers to antibody generation) to biologically validate their assertions that the sequence of the present invention has utility as drug targets for human disease (specification at page 1, lines 27-31 enumerates many diseases).

Reply One skilled in the art, however, is not able to find corroboration of such uses of methods from page 2 and 17 to demonstrate utility of disclosed sequences as drug targets in any of human diseases from page 1.

III. On page 4, line 26 and further, of the Brief Appellants invite the Board's attention to the fact:

"that a sequence that is identical at the amino acid level over the entire length of the described sequence is present in the leading scientific repository for biological sequence data (GeneBank), and has been annotated by third part scientists wholly unaffiliated with Appellants as neurolysin (Homo sapiens) (GenBank accession number: CAC27329, alignment and GenBank report provided in Exhibit A). Therefore, it is clear that the amino acid sequence of SEQ ID NO: 2 encodes human neurolysin. Furthermore, Appellants would like to invite the Board' attention to the fact that GenBank Accession No. AJ300837 (alignment and GenBAnk report provided in Exhibit B) that describes a sequence annotated by others to be the mRNA for human neurolysin has a 99% identity with the nucleic acid sequence of SEQ ID NO: 1 (2113 of a total of 2115 bases present in SEQ ID NO:1). These sequences have also been defined by third party scientists, wholly unaffiliated with Appellants, as encoding human neurolysin. Given this clear evidence that

those skilled in the art have independently accepted the utility described in the present specification, there can be no question that *Appellants' asserted utility* [emphasis added] for the described sequences is 'credible...

Clearly evidence supports Appellants' assertion that the sequence of the present invention encode a novel human metalloprotease (specifically neurolysin, metallopeptidase M3 [emphasis added]) which has a well established utility that is recognized by those of skill in the art."

Reply Firstly, is important to remind that the specification's phrase "sharing sequence similarity with mammalian neurolysin proteins" is not an assertion of function, but it refers to the structure of the claimed chemical compound. At the time application was filed the function of neurolysin was well established for mammals, as Applicants proved by the content of the IDS, however at the time of filing a human neurolysin had not been identified. The characteristic feature of neurolysin is that it cleaves neurotensin between residues Pro10 and Tyr11, and that it binds angiotensin. However, Applicants themselves did not present any evidence that protein of SEQ ID NO: 2 is able to cleavage neurotensin between residues Pro10 and Tyr11, and to bind angiotensin, nor did they assert that the new gene they disclose encodes a human neurolysin. In conclusion, as indicated above, the assertion of the function is lacking in the specification. Secondly, the fact that the third party scientists cloned a very similar human gene and annotated it as neurolysin after the Applicant filed the application does not change the fact that the protein of SEQ ID NO: 2 encoded by DNA of SEQ ID NO: 1 was disclosed by Applicants without asserting its utility. Appellants are reminded that Chen et al., who deposited the protein having the accession No. CAC27329 have, thus

far, not disclosed actual enzymatic activity of the protein set forth by SEQ ID NO: 2 that is encoded by SEQ ID NO: 1, and which they call neurolysin. Search indicates that disclosure of the protein having the accession No. CAC27329 has not been followed by any publication by Chen or his co-workers showing that this sequence does in fact have neurolysin activity. Thus, all what is currently known of "human neurolysin" is a DNA and amino acid sequence which shows structural homology to pig, rat, mouse and rabbit enzyme. Independently of lack of records of biological activity of the sequence having accession number CAC27329, the availability of post-filing date evidence of utility is irrelevant in the instant situation, where Applicants' specification lacks any assertion of this utility in the specification. While post-filing evidence can be used to show that an assertion was correct, the assertion must have been present at the time of filing.

Appelants statement at the end of the above quoted fragment of the Appeal brief contains the term "metalloprotease M3" that is absent from the specification.

IV. Appellants argue that the present case is similar to that discussed in Example 10 of the Utility Guidelines and state,

> "Example 10 of the PTO's Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. §101 as allegedly lacking a patentable utility and under 35 U.S.C. §112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utiity, is not proper when there is no reason to doubt the asserted utility of a full length sequence (such as the presently claimed sequence) that has a similarity to a protein having a known function. In the Analysis portion of Example 10 it states that 'Based on applicant's

disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID: 2 encodes ligase", page 5, line 21 of Appeal Brief.

Appellants continue their arguments saying, ".....Note that if there is a well–established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed..... Thus the conclusion reached form this analysis is that a 35 U.S.C § 101 and 35 U.S.C. § 112 first paragraph, utility rejection should not be made", page 6 line 1.

However Example 10 of the utility Guidelines to which Appellants are referring to is proper in the case when Applicants' specification provides the assertion of the utility of the claimed sequence. This, however, is not the case in the instant application. The specification of the instant application did not make an assertion of function based on the disclosed structural similarities of the novel protein taught to previously known proteins. In the instant case the situation is not analogous to that in Example 10. The utility associated with the claimed invention is not asserted in the specification which was crucial in Example 10.

While it is true that if there is a well-established utility for a compound known in the art the utility need not be established in the specification, there is no well-established utility for the instantly claimed gene. Applicants statement that neurolysin has a well estabilished utility is noted but is irrelevant to the instant situation in which the specification did not assert that the disclosed protein is a neurolysin. An invention has a well-established utility if a person of ordinary skill in the art would immediately appreciate why the invention is useful basaed on the characteristics of the invention (see MPEP 2107). The specification merely asserts that the disclosed protein is a metalloprotease not that it is a neurolysin. There is no well-established utility for

metalloproteases as each member of this broad general class of compounds acts on different protein substrate. Thus the skilled artisan does not know instantly how to use any protein disclosed as a metalloprotease as would be necessary for this to be considered a well–established utility. Thus there is no well established utility for the instantly disclosed gene.

V. Appellants' opinion is that "the biological significance and function of neurolysin and neurolysin like metalloproteases are well known to those in the art", page 6, third paragraph. As an evidence Appellants quote Exhibits C, D and E.

Reply The Exhibits do not support Appellants' opinion, because:

1. nowhere in Exhibit C one can find the word "neurolysin",
2. Exibits D and E are articles that were published in 2002 and 2003, i.e. after filing the instant application in 2001.

VI. Summarizing, Appellant conclude, "in spite of the many publication to the contrary, the utility of neurolysin remains to be established to the Examiner's satisfaction", page 7, end of the first paragraph.

Reply This conclusion misses the point with regard to the claimed polypeptide. Although the utility of animal neurolysins was already known before the instant application was filed, Appellants have not known at the time the application was filed if their invention was a neurolysin. This is important since, if information regarding the biological role of the claimed invention were to be presented, a credible, substantial and

specific utility could be apparent for the claimed polypeptide, such as cleavage of neurotensin, screening chemicals for modifiers of this process, and diagnosing abnormalities of the process in human diseases. However, without any connection disclosed in the specification the art knowledge about other mammalian neurolysins does not establish utility for the disclosed human gene.

VII. In the second paragraph of page 7 Appellants, address examiner's argument regarding lack of disclosure of enzymatic activity of the claimed protein, i.e. cleavage of neurotensin, "Appellants assertion of the stated utility is legally sufficient and should control the utility analysis, unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Appellant asserted utility."

Reply This argument is not persuading. Since there is no assertion of utility in the specification, the key factor controlling the utility analysis is missing. While the examiner bears the burden of refuting any assertion of utility, Appellants are required to make the assertion unless the invention has a well established utility. Appellants have not made nay assertion in the instant application and as discussed above there is no well –established utility in the instant situation.

VIII. In the last paragraph on page 7 Appellants emphasize,

"In the response to the Final Action, Appellants submitted still further evidence of finding supporting the real word utility of the metalloprotese encoded by the sequences of the present invention as provided by Appellants findings involving the analysis of transgenic 'knockout' mice, in which the function of the gene encoding the sequences of the present invention were disrupted in embryonic stem cells..... Disruption

> of the mouse gene of the present invention and thus elimination of the protein it encodes, resulted in an increased anxiety-like response..... decreased sensivity to pain.... decrease heart rate when compared to gender-matched littermates and the historical mean. This clearly provides evidence that the nucleic acid and protein of the present invention have a biological function and the molecules of the present invention as well as agonist or antagonists directed at them can be used to diagnose and treat anxiety and pain disorders as well as cardiac disease."

Reply It is unclear whose results are the Appellants referring to in their analyses. Appellants themselves did not describe these results in the specification, neither as their own nor by quoting the other authors. Applicant's response to Final Action was filed in April 2003, i.e. two years after filing the application. Appellants' argument it is found not persuasive, because biological role of the claimed gene described in the above passage was unknown at the time application was filed. Furthermore, it should be noted that the above discussed knockout mutations are of a mouse gene, yet the claimed gene is a human gene. How could mouse knockout mutants establish utility of a human gene?

IX. Appellants argue that (page 8, line 26) the statement of the Advisory Action that the specification lacks any assertion of utility as neurolysin because the Appellant have no proved it or at least asserted it

> "contradicts the position presented in Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55), 'Note that if there is well established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed...", (page 8, line 26).

Reply This argument is found not persuasive, because there is no well-established utility already associated with SEQ ID NO: 1 which is the claimed invention.

Although the genes encoding neurolysins of several animal species were cloned and the function of the encoded protein were established, one skilled in the art could not recognize, at the first sight, the polynucleotide of SEQ ID NO: 1 as encoding human neurolysin and the Appellants have neither proved it nor asserted it.

X. Furthermore Appellant emphasize, "The Examiner does not appear to accept the Appellant's assertion that the sequences of the present invention encode a novel human metalloprotease specifically metalloprotease M3, neurolysin", page 9 line 10.

Reply First of all the term "metalloprotease" is a generic term that covers thousands of enzymes, thus the term "metalloprotease" used alone cannot identify a particular metalloprotease and its specificity which is related to its specific use. Furthermore, as indicated above, nowhere in the specification do Applicants state that the novel protein is neurolysin, and the term metalloprotease M3 is absent from the disclosure. Applicants use the term "neurolysin, metallopeptidase M3 family" for the first time in Amendment and Response to the Final Office Action filed April 29, 2003, which is two years after filing the instant application.

XI. In the last paragraph on page 9 of the brief Appellants indicate that the skilled artisan would readily appreciate the utilities of the present invention "associated with diseases that have been linked to the novel human metalloprotease, neurolysin. Therefore, the present utility rejection must fail."

Reply The appreciation of the utilities associated with diseases that have been linked to the claimed invention is not possible, because none of diseases has been linked to the function of the claimed polypeptide. The specification is silent in regard to any abnormalities in human physiology that are associated with biological function of protein of SEQ ID NO: 2, because the function has not been established. Those skilled in the art do not know which syndromes are associated with mutations in claimed polynucleotide or with abnormal expression of the claimed polynucleotide in human body. Further experimentation is necessary to determine the biological function of polypeptide encoded by polynucleotide of SEQ ID NO:1 and to find which diseases are associated with deficiency of the encoded protein. Thus, the utilities of the present invention associated with any human disease are not substantial; they do not constitute "real world" context of use because they necessitate basic research to determine the properties or the mechanisms in which the claimed product is involved; see examples (A) and (B) of MPEP § 2107.01, page 2100-33.

XII. It is Appellant's opinion that the present polynucleotides are candidates for assessing gene expression using DNA chip assay (the first paragraph, page 10) and that "knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip." Furthermore, according to Appellants, extensive utility for molecules encoded by claimed polynucleotide described thus far in the Appeal Brief constitute an evidence that claimed sequences provide specific marker of

the gene encoding neurolysin and, thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using DNA chips. Appellants assert that DNA chips have utility as evidenced by hundreds of issued patents and submit examples of such patents in Exhibits F, G, H, I, J and K and argue that the present polynucleotides have a specific utility for analyzing gene expression in DNA chip assays. Appellants conclude by stating that a statement of utility in the specification must be accepted absent reasons why one of skill in the art would have reason to doubt the objective truth of such statement.

Reply Appellant's arguments in regard to utility of the claimed polynucleotides in DNA chips have not been found persuasive. While it is agreed that the use of polynucleotides in DNA chips (microarrays) is widespread and that the claimed polynucleotides can be attached to DNA chips, for the claimed polynucleotides to be specifically useful in such application, one would require some knowledge or guidance as to the biological role of the polypeptide encoded by such polynucleotides to effectively use the information gathered in tracking the expression patterns of such polynucleotides. The reduction or increase in expression of a polynucleotide is meaningless unless one can link changes in expression with some biological function. For example, if one were to use the claimed polynucleotides in assays which would lead to the discovery of drugs of a specific condition, such as an assay which uses a DNA chip to evaluate expression patterns upon exposure to a test compound, one need to

know which diseases and/or biological functions are associated with the expression of such polynucleotides. Otherwise, one of skill in the art would have to carry out further experimentation to determine which are the conditions (i.e. diseases) and/or biological functions associated with the claimed polynucleotides.

Appellant's proposal of utility of the claimed polynucleotides as specific markers which are targets for discovering drugs associated with human disease is absent from the specification and even if it were taught it would have not been a specific and substantial utility since the specification is silent in regard to biological function and any syndrome(s) which is associated with mutations in and/or expression of the claimed polynucleotide.

The Examiner acknowledges the issued patents related to DNA chips, however it is noted that the instant claims are not drawn to methods of use of DNA chips or to DNA chips (microarrays) but rather to specific polynucleotides. Furthermore, as Examiner indicated in her Office Actions, the asserted use of the claimed polynucleotides in DNA chips is generic. The fact that only 2-4% of genomic DNA is expressed does not make use of expressed sequences in DNA chip format specific. Appellants have stated, many other polynucleotides including those in the public domain can and are used in DNA chips.

XIII. On page 12, the first paragraph of the Brief, Appellants argue that further evidence of "real world" substantial utility, is the fact that there is an entire industry established based on the use of polynucleotides (i.e. gene

sequences) or fragments thereof in a gene chip format. Appellants further recite the many companies involved in the manufacture of DNA chips (i.e. gene chips or microarrays) and companies which at some point or another concentrated on the use of polynucleotides or fragments. Since large amounts of money were paid by large pharmaceutical companies to purchase companies which deal with DNA chips, polynucleotides and fragments, Appellants argue that it is clear that the use of polynucleotides (i.e. gene sequences) or fragments is a "real world" substantial, widespread and well-established utility. Furthermore, Appellants argue that one of skill in the art as well as venture capitalists and investors can recognize the utility of genomic data in general, and specifically human genomic data. Appellants submit articles by Venter et al. and Jasny et al. in Exhibits I and J, respectively, to support their argument that the usefulness of human genomic data, including the claimed polynucleotides, is substantial and credible, since it is worth billions of dollars and has resulted in the creation of many companies, and well-established, since the utility of human genomic information has been clearly understood for many years.

Reply While it is agreed that (1) there is an industry based on the use of polynucleotides and fragments, (2) there are many billions of dollars invested in companies which use DNA chips and related technologies, (3) billions of dollars have been spent in the generation of human genomic data, and (4) the utility of human

genomic data has been understood for many years, Appellant's arguments have not been found persuasive for the following reasons. First, it is noted that it is the patentable utility of the specific polynucleotides claimed in the instant application and not the general utility of DNA chips and usefulness of genomic which is being determined and discussed. The Examiner is not disputing the patentable utility of DNA chips as a collection of polynucleotides linked to a solid support but rather the patentable utility of specific polynucleotides encoding an alleged human neurolysin. Furthermore, the Examiner is not disputing that one of skill in the art can see the potential usefulness of information coming out of the human genome project, however it is also known in the art that this information is valuable to the extent that it provides a starting point for scientists to further investigate the biological significance of the genetic information collected and possibly discover how to treat many conditions and diseases. In fact, while the potential usefulness of human genomic data was enormous, the lack of an immediate use for human genomic data was the primary reason why it was the federal government and not a private entity who first provided funding for the Human Genome Project. While it is agreed that the disclosure of an additional human polynucleotide provides more information in regard to the human genome, as indicated previously, in the absence of any additional information in regard to its biological function, the isolation of the human polynucleotides of the instant application is only useful as a starting point for researchers to further investigate its biological significance, therefore the utility of the instant polynucleotides, as clearly stated in MPEP § 2107.01 is not a "real world" substantial utility.

XIV. In the second paragraph on page 12 Appellants refer to the use of polymorphisms of the claimed polypeptides in identification of paternity and forensic analysis. Appellants submit, referring to page 16, line 21-28 of the specification, "in the worst case scenario, the described polymorphisms are each useful to distinguish 50% of the population (in other words, the marker being present in half of the population)".

Reply Firstly, as indicated above, the polymorphism of SEQ ID NO: 1 is indicated on page 15 and not 16. Secondly, the specification fails to specifically assert a utiliy for the recited polynucleotide in forensic analysis and the worst case scenario is not referred to in the specification. Even if the specification did make such an assertion, use of the claimed polynucleotides in forensic analysis would not satisfy the requirement for utility under 35 USC 101. Use of the claimed polynucleotides in forensics would not constitute a "real world use" as Applicants have not identified any particular reason for analysis of the particular polymorphism disclosed or any particular benefit that would derive from analysis of said polymorphisms. Based on Appellants' disclosure, one of skill in the art would not be motivated to use the recited nucleic acid molecules in forensic analysis.

In conclusion, this utility cannot be considered substantial, because further research is necessary before implementation of polymorphism of SEQ ID NO: 1 or 3 in forensic studies. Such a use would be also not specific, as the presence of polymorphisms in human DNA is well established, and single nucleotide polymorphism occurs approximately once every 100 to 300 bases (NCBI, 2000). Thus, any locus on a

human chromosome will exhibit one or more polymorphisms, which could be used in forensic analysis.

XV. According to the Appellant, the examiner is clearly confusing the requirement for a specific utility with the requirement for a unique utility (page 13, line 19 of the Appeal Brief). If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on bateries, automobile tires, golf balls, golf clubs, and treatment for a variety of human diseases, as the utilityof each of these compositions is applicable to the broad class in which each of these compositions falls.

Reply Appellant have never been asked to identify a utility that is unique, i.e. not shared by another compounds or composition. Rather, Appellants have been required to identify a utility that is specific to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention. See, e.g., Brenner, 383 U.S. at 534,148 USPTQ at 695 (An invention does not have utility sufficient to satisfy §101 until it is "refined and developed" to the point of providing a specific benefit in currently available form.) An invention certainly can have a utility that is shared by other compound or compositions. On the other hand, not every utility will satisfy §101, even if the utility is shared by a class of inventions. So, while a utility need not be unique to a claimed invention, it must nonetheless be specific, and in currently form, in order to satisfy §101. For example, Appellants argue above the claimed polynucleotide

can be used as a polymorphic marker in forensic analysis. However, any observed results of the presence or absence of the claimed polymorphism would have no meaning without additional knowledge of what the significance of this sequence variation is. The specification in effect discloses that the claimed products include a polymorphic site and leaves those of skill in the art to figure out what to do with it. This utility is not substantial; it does not provide a specific benefit in currently available form.

XVI. It is Appellants notion that the claimed polynucleotides have specific utility "in determining the genomic structure of the corresponding human chromosome (specification at page 11, lines 5-11), for example, mapping the protein encoding regions as described in the specification (page 11, lines 11-17)", page 14 line 20 of the Appeal Brief.

Reply. The specification fails assert the use the claimed polynucleotide in determining the genomic structure and mapping the protein on the corresponding human chromosome. The terms "genomic structure", "mapping", "localizing" are not used in the specification and the chromosome on which the claimed polynucleotide resides is unknown. The quoted passage of the specification refers to determination of the full length cDNA, including flanking regions.

XVII. On page 15, line and further, Appellants remind the Board that only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences, and that the presently claimed

polynucleotide sequences provides biologically validated empirical data (e.g. showing which sequences are transcribed, spliced, and polyadenylated), which specifically define the portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (i.e., the described sequences are useful for functionally defining exon splice-junctions). The Appellants respectfully submit that the practical scientific value of expressed, spliced and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Appellants further direct the Board's attention to an article by Venter et al., pages 1317-1321, which discusses the significance of expressed sequence information in the structural analysis of genomic data. Appellants conclude that since their polynucleotides define biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

Reply While it is agreed that (1) only a small portion of the genome contains exons and (2) ESTs (expressed sequence tags) as disclosed by Venter et al. are of great significance in the analysis of genomic data specifically in the area of gene prediction and function annotation, it is unclear how the claimed polynucleotides provide biologically validated data for the following reasons. As known in the art and also

discussed in Venter et al. pages 1317-1321, automated gene annotation (i.e. computer-based annotation of function based on sequence homology) uses among other things, ESTs (partial sequences of expressed genes) as one of the tools to identify and annotate genes and their corresponding cDNAs (i.e. transcripts which encode proteins and lack introns). The information provided by ESTs along with protein similarity data is used to assemble cDNAs. There is no polynucleotides (cDNA since they encode the polypeptide of SEQ ID NO: 2) may have been assembled with the use of ESTs. As such, there is no assurance that the assembled cDNA encoding the polypeptide of SEQ ID NO: 2 is indeed an actual transcript of a gene since it is known in the art that computer-based assembly of genes and their transcripts (cDNA) is not perfect and may lead to wrong splicing of genes. In fact, Venter et al., page 1320, second column, last paragraph, indicates that their annotation algorithm (Otto), in the absence of the corresponding experimental evidence, has in some cases incorrectly predicted gene splicing and the wrong transcript has been predicted. Since Appellants provide no experimental evidence to corroborate that the claimed polynucleotides are indeed the actual transcripts of a gene, one cannot reasonably conclude that the claimed polynucleotides provide biologically validated data.

XVIII. On page 15, second paragraph, Applicants emphasize,

> "As still further evidence supporting Appellants assertion of the specific utility of the sequences of the present invention in localizing the specific

region of the human chromosome and identification of functionally active intron-exon splice junction is the information provided in **Exhibit N**. [Exhibit N presents result of Blast analysis indicating the sequence of the present invention is encoded by 13 exons spreading non-contiguously along a region of human chromosome 5]."

Reply Nowhere in the specification do Appellants provide such assertion. At the time the application was filed Appellants did not consider such utility of SEQ ID NO: 1. In addition, as known in the art, any human polynucleotide that encodes a protein can be used to detect its own locus on a chromosome and to map the exons within the gene. Therefore, this use is generic, and not specific.

XIX. On page 16, first paragraph, Applicants state that the sequences of the present invention and neurolysin (NLN), map to the same locus, 5.q12.2.

Reply These results are not taught by the specification, and is unclear to whose results Appellants refer. The fact that two encoding DNA are located in the same chromosome band does not mean that they both encode the same protein. The chromosome 5 master map indicates two (as located and registered by May 6, 2004) genes in 5q12.2, a hypotetical protein LOC91942 and importin 11; see the attached NCBI printout. Obviously not only neurolysin is located in 5q12.2.

XX. On page 16 Appellants also remind the examination Guidelines for the Utility Requirement,

> "if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a 'specific and substantial utility') and the assertion would be considered credible by a person of ordinary skill in the art, the examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001)."

Reply While an assertion for any particular purpose which has a "specific and substantial utility" is credible to the examiner, there is no such assertion in the specification. Applicants assert utilities that are not specific and substantial, for example, use of the disclosed DNA molecules in DNA chip assay; see the discussion above. Thus, the assertion of use of the disclosed DNA molecules in DNA chip assay cannot provide a patentable utility because it lacks the necessary feature of being "specific and substantial" i.e. does not meet the requirement stated by 66 Federal Register 1098, Jan. 5, 2001 as quoted by Appellants.

XXI. On page 16 and 17 of the Brief, Appellants argue that in *In re Brana*, the Federal Circuit admonished the PTO for confusing the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human

consumption. Appellants recite part of the decision and emphasize that the Federal Circuit referred to utility within the context of 35 USC § 101 and usefulness within the context of 35 USC § 112, first paragraph. Appellants specifically emphasize a statement of *In re Brana* which reads "usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development". In Appellant's opinion, the need for experimentation does not render the claimed invention unpatentable and they state that a considerable amount of experimentation is permissible so long as such experimentation is routinely practiced in the art. Appellants further argue that according to *In re Wands*, a patent need not to disclose what is well known in the art.

Reply While it is agreed that FDA approval is not a requirement for finding a compound patentably useful and that necessity of routine experimentation does not render an invention unpatentable, it is noted that in the instant case, the utility rejection was not applied to the claimed invention because it failed to comply with government requirements to market the invention for human consumption or because some routine experimentation is required to practice the claimed invention. Instead, the utility rejection was applied due to the lack of assertion or determination of its biological function as already discussed. Determination of biological function of a new protein is a multistep and tedious wok and it is not reasonable for one of skill in the art to conclude that the additional research required to practice the claimed invention is merely routine.

In regard to *In re Wands*, while it is agreed that one need not disclose what is well known in the art, it is noted that neither the specification nor the state of the art describe or provide any information as to the actual biological function of the polypeptide encoded by the claimed polynucleotides other than to indicate that the polypeptide of the instant invention is a metalloprotease. Since information which would enable one of skill in the art to practice the claimed invention is not known in the art, it is the specification which must provide the necessary information to enable the skilled artisan to practice the claimed invention.

XXII. At the beginning of page 18, Appellants indicate that while they are aware of the new utility guidelines set forth by the USPTO, the current rules and regulations are the patent laws set forth in 35 USC and the rules set forth in 37 CFR but not the Manual of Patent Examination Procedure (MPEP) set forth by the USPTO. Furthermore, Appellants argue that it is the job of the judiciary and not the USPTO to interpret these laws and rules. Appellants argue that there are no recent changes in either 35 USC § 101 or in the interpretation of 35 USC § 101 by the Supreme Court or the Federal Circuit which support the new utility guidelines set forth by the USPTO and submit examples of US patents in Exhibit O, P, Q and R which, according to Appellants, do not comply with the new utility guidelines. While Appellants admit that each application is examined on its own merits, Appellants conclude that holding them to a different standard of utility is a clear violation of due process because of the

similarity in subject matter between the claimed invention and the inventions in US patents of Exhibit O, P, Q, and R. Appellants conclude that holding Appellants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

Reply Appellants are reminded that the Examiner must examine a patent application according to the guidelines set forth by the USPTO as well as the MPEP, since the Examiner has no authority to disregard such guidelines or to apply her own interpretation of patent law in the examination of the application. Furthermore, as set forth in the guidelines and the MPEP, the guidelines were promulgated by the PTO in accordance with all applicable case law and thus are believed to be consistent therewith. While the Examiner acknowledges the US patents of Exhibits O, P, Q and R, each application is examined on its own merits according to the current guidelines of examination as set forth by the USPTO and a discussion on the utility of any polynucleotide claimed in such patents would require a detailed review of the record of each individual case, which would be improper herein. Finally, Appellants are further reminded that the Examiner has no authority to comment in regard to the legality of the new utility guidelines or the MPEP as set forth by the USPTO.

B. Are Claims 1-5 unusable due to a lack of patentable utility?

In the second paragraph of this section Appellants indicate that arguments detailed in section VIII(A) of the Brief are incorporated by reference due to the fact that it

has been determined by the courts that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph have the same basis, specifically the disclosure of a credible utility. Appellants argue that since claims 1-5 have been shown to have a "specific, substantial and credible utility" as indicated in section VIII(A), the present rejections under 35 USC 112, first paragraph cannot stand and must be overruled.

As indicated by Appellants, the how to use requirement of Section 112 first paragraph has the same basis that the utility requirement of Section 101; rejection under section 112, first paragraph, may be affirmed on the same basis as lack of the utility rejection under section 112 . See, e.g. *In re Swartz*, 56 USPTQ2d 1703 (Fed. Cir. 2000*); In re Kirk,* 153 USPQ 48 (CCPA 1967).

In conclusion, although Appellants' arguments and exhibits have been fully and carefully considered, for reasons set forth above they are not considered sufficient to rebut the prima facie case of lack of utility and it is believed that the rejections should be sustained.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Art Unit 1652